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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n 6 : C07D 235/20, A61K 31/41

A1

(11) Internati nal Publication Number: WO 95/08540

(43) Internati nal Publication Date: 30 March 1995 (30.03.95)

(21) International Application Number: PCT/GB94/02051

(22) International Filing Date: 21 September 1994 (21.09.94)

(30) Priority Data:

125,466	22 September 1993 (22.09.93)	US
232,915	25 April 1994 (25.04.94)	US

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(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published

With international search report.

(54) Title: BIS(AMIDINOBENZIMIDAZOLYL)ALKANES AS ANTIVIRAL AGENTS

(57) Abstract

The present invention relates to certain bisbenzimidazole compounds and their use in medical therapy, particularly in the treatment of immunodeficiency virus infections. Also provided are pharmaceutical formulations and processes for the preparation of compounds according to the invention.

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BIS(AMIDINOBENZIMIDAZOLYL)ALKANES AS ANTIVIRAL AGENTS

The present invention relates to certain bisbenzimidazole compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy, particularly the prophylactic and acute treatment of certain protozoal and viral infections.

In the field of antiviral chemotherapy, few drugs exist which effectively combat the virus per se, owing to the difficulty of attacking the virus while leaving uninfected host cells unimpaired. It has been established that certain stages in the virus replicative cycle offer possible targets for antiviral therapy. These stages may prove susceptible to attack where they differ sufficiently from any corresponding host-cell function. However, owing to great similarity between viral and host functions, effective treatments have proved very difficult to identify.

One group of viral pathogens which has assumed a particular importance is the retroviruses. Retroviruses form a sub-group of RNA viruses which, in order to replicate, must first 'reverse transcribe' the RNA of their genome into DNA ('transcription' conventionally describes the synthesis of RNA from DNA). Once in the form of DNA, the viral genome may be incorporated into the host cell genome by a viral integrase enzyme, allowing it to take advantage of the host cell's transcription/translation machinery for the purposes of replication. Once incorporated, the viral DNA is virtually indistinguishable from the host's DNA and, in this state, the virus producing mechanism may persist for the life of the cell.

Species of retroviruses, the Human Immunodeficiency Viruses (HIVs), have been reproducibly isolated from humans with Acquired Immune Deficiency Syndrome (AIDS) or with the symptoms that frequently precede AIDS. AIDS is an immunosuppressive or immunodestructive disease that predisposes subjects to fatal opportunistic infections. Characteristically, AIDS is associated with a progressive depletion of T-cells, especially the helper-inducer subset bearing the OKT4 surface marker. HIV is cytopathic and appears to preferentially infect and destroy T-cells bearing the OKT4 marker, and it is now generally recognised that HIV is the aetiological agent of AIDS.

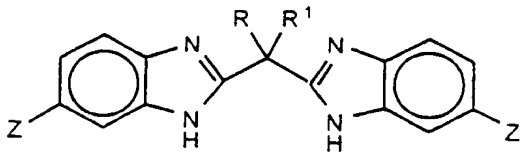
Simian Immunodeficiency Virsuses (SIVs) are morphologically similar and biologically related to the HIVs. They infect certain monkeys, and experimental SIV infection in macaques causes wasting syndromes and discaso similar to AIDS. Infection of a human with SIV has been reported by Khabbaz et al. N. Engl. J. Med., 330 (3), 172-77 (1994).

Feline Immunodeficiency Virus (FIV) infects cats, leading to immune system depression and persistent secondary infections. First isolated in 1986 from a cat with an AIDS-like disease, FIV has many characteristics in common with HIV (Miyazawa et al., J. Vet. Med. Sci., 55 (4), 519-26 (1993)).

We have now identified certain bisbenzimidazole compounds and salts thereof which have unexpectedly been found suitable for use as antiviral agents. They also have utility as antiprotozoal agents.

Tidwell, R.R. et al., Antimicrob. Agents Chemother., 37(8), 1713-16 (1993) and PCT Patent Specification WO94/08580 describe a series of bis-benzimidazoles, including 2,2'-methylenebis(5-(2-imidazolin-2-yl)-1H-benzimidazole), active against *Pneumocystis carinii*. A series of bisamidinobenzimidazoles exhibit DNA minor groove binding (Fairley, T.A. et al., J. Med. Chem., 36(12), 1746-53 (1993)). Geratz, J.D. et al., Am. J. Pathol., 139(4), 921-31 (1991) describe the anti-inflammatory activity of trans-bis(5-amidino-2-benzimidazolyl)ethene and its congeners.

According to a first aspect of the present invention there is provided a compound of formula (I)



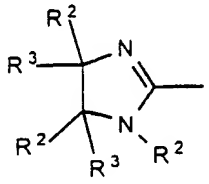
(I)

wherein,

R and R^1, which may be the same or different, are hydrogen, fluoro, hydroxyl, amino, C_{1-6} alkoxy, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl;

Z is selected from a group consisting of

(a)



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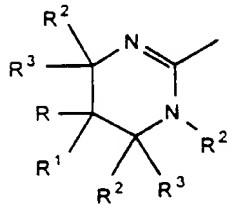

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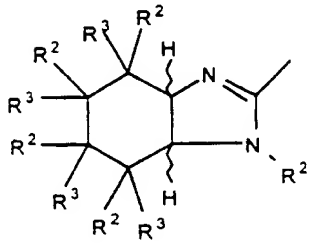
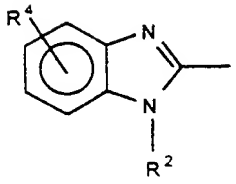
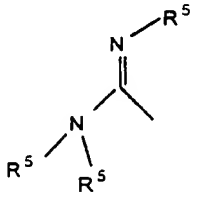


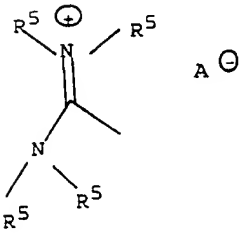
(d)

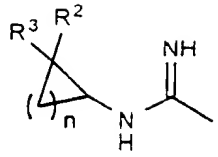


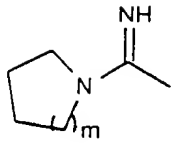
(e)

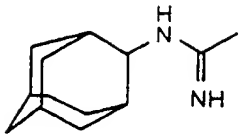


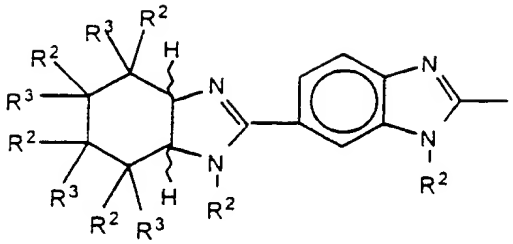
(e)^1

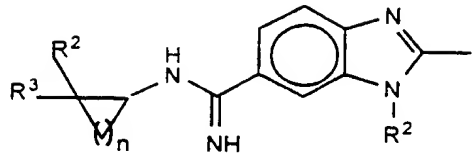


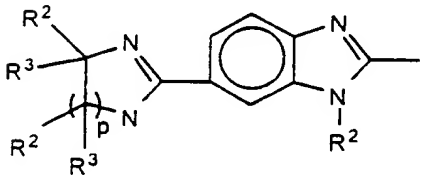
(f) 

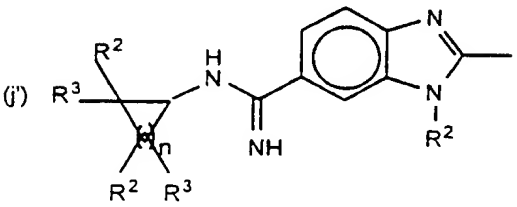
(g) 

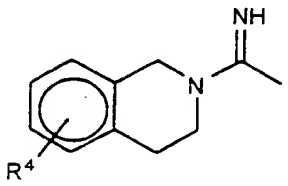
(h) 

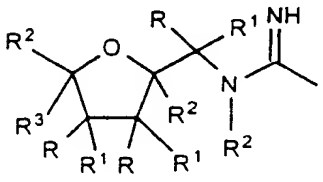
(i) 

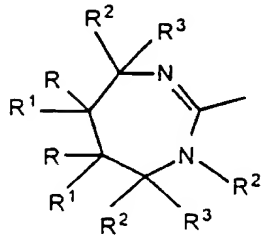
(j) 

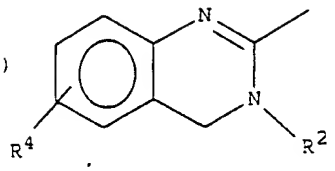
(k) 

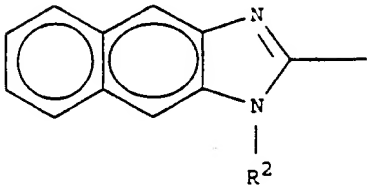
(j') 

(l) 

(m) 

(n) 

(o) 

(p) 

wherein

m is 0, 1 or 2;

n is 1, 2, 3, 4 or 5;

p is 1, 2 or 3;

R^2 and R^3, which may be the same or different, are hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl, phenyl, -COOH, -$COOR^{2a}$, -$CON(R^{2a})_2$ or -$(CH_2)_nX\ R^{2a}$ (wherein R^{2a} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl, n is 1,2,3,4 or 5 and X is as defined below);

R^4 is hydrogen, halo, amino, C_{1-4} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl;

R^5, which may each be the same or different, is C_{1-6} alkyl substituted by one or more phenyl groups (e.g. diphenylmethyl) or by a heterocyclic group comprising a 5- or 6-membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of O, N and S (e.g. furyl, pyranyl, pyrrolyl, imidazolyl, pyridyl,

pyrazinyl, piperidinyl, morpholinyl or pyrimidinyl) optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, amino, nitro or halo; C_{3-7} cycloalkyl; C_{2-6} alkenyl; phenyl; hydrogen; or a C_{3-7} carbocyclic ring optionally substituted by R^2 and R^3 (wherein R^2 and R^3 are as hereinbefore defined); provided that the R^5 groups are not all hydrogen;

R^6, which may each be the same or different, is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or $-(CH_2)n\ X\ R^2$ wherein n and R^2 are as hereinbefore defined;

X is O, S or NH;

A^- is a physiologically acceptable anion e.g.
halide (Cl^-, F^-, Br^-, I^-), biphosphate ($H_2\ PO_4^-$), triflate ($OSO_2\ CF_3^-$), mesylate ($OSO_2CH_3^-$), tosylate ($p\text{-}CH_3C_6H_4SO_3^-$) or bisulfate ($HSO_4^-$);

R and R^1 (in formulas (b), (n), (m), and (r)) are as hereinbefore defined;

with the provisos that (i) when Z is (a) or (b), R and R^1 (in formula (b)) and R^2 and R^3 are not all hydrogen; (ii) when Z is (n), R, R^1, R^2 and R^3 are not all hydrogen;

or a pharmaceutically acceptable salt thereof; or a physiologically functional derivative thereof.

A sub-class (IA) of compounds within the scope of the present invention comprises compounds of formula (I) wherein R and R^1, which may be the same or different, are hydrogen, fluoro, hydroxyl, amino, C_{1-6} alkoxy, C_{1-6} alkyl or phenyl;

Z is selected from a group consisting of formulae (a), (b), (c), (d) and (e) above:-

wherein

R^2 and R^3, which may be the same or different, are hydrogen, C_{1-6} alkyl or phenyl;

R^4 is hydrogen, halo, amino, C_{1-4} alkoxy, C_{1-6} alkyl or phenyl;

R^5, which may be the same or different. is phenyl or hydrogen provided that all R^5 groups are not hydrogen: and

R and R^1 are hydrogen. fluoro, hydroxyl. amino. C_{1-6} alkoxy, C_{1-6} alkyl or phenyl;

with the provisos that (i) when Z is (a), and R^2 and R^3 are hydrogen, R and R^1 are not both hydrogen; and (ii) when Z is (c), R^2 and R^3 are hydrogen;

or a pharmaceutically acceptable salt thereof; or a physiologically functional derivative thereof.

A further sub-class (IB) of compounds within the scope of the invention comprises compounds of formula (I) wherein R and R^1 which may be the same or different are hydrogen, fluoro, hydroxyl, amino, C_{1-6} alkoxy, C_{1-6} alkyl, phenyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl C_{1-6} alkyl;

Z is selected from the group consisting of formulae (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k) and (l) above:-

wherein

m is 0, 1 or 2;

n is 1,2,3,4 or 5;

p is 1,2 or 3;

R^2 and R^3 which may be the same or different, are hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl;

R^4 is hydrogen, halo, amino, C_{1-4} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl; and

R^5 which may be the same or different, is C_{1-6} alkyl substituted by one or more phenyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, phenyl or hydrogen provided that all R^5 groups are not hydrogen;

with the proviso that when Z is (a) and R^2 and R^3 are hydrogen, R and R^1 are not both hydrogen;

or a pharmaceutically acceptable salt thereof; or a physiologically functional derivative thereof.

By the term "alkyl" is meant a saturated or unsaturated, straight or branched chain group

By the term "phenyl" is meant a phenyl group, optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, amino, nitro or halo.

By the term "halo" is meant fluoro, chloro, bromo or iodo.

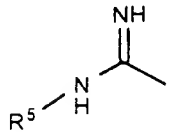
The compounds of formula (I) may include tautomers as well as a number of asymmetric centers in the molecule depending on the precise selection of various substituents. Formula (I) is intended to include all possible tautomers and stereoisomers, e.g., diastereoisomers and enantiomers.

Preferred compounds of formula (I) are those wherein Z is (a), (b) or (e), especially (e), and those wherein R and R^1 are both hydrogen.

When Z is (a), the groups R^2 and R^3 are preferably hydrogen or C_{1-6} alkyl, especially methyl or ethyl.

When Z is (b), the groups R and R^1 (in formula (b)) are preferably C_{1-6} alkyl, e.g. methyl, and/or the groups R^2 and R^3 are each hydrogen.

When Z is (e) the group is preferably of formula



wherein R^5 is a C_{3-7} cycloalkyl group e.g. a cyclopentyl group, or a heterocyclic C_{1-6} alkyl group, e.g. a tetrahydro-2-furfuryl group

Illustrative compounds of the invention within the scope of general formula (I) include:

2,2'-(fluoromethylene)bis(5-(2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-(difluoromethylene)bis(5-(2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-methylenebis(5-(4-methyl-2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-methylenebis(5-(3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole);
2,2'-ethylidenebis(5-(2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-isopropylidenebis(5-(2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-methylenebis(5-(3,4,5,6-tetrahydro-2-pyrimidinyl)-1H-benzimidazole);
2,2'-methylenebis(5-(1-methyl-2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-methylenebis(N^2-ethyl-1H-benzimidazole-5-carboxamidine);
2,2'-methylenebis(N-cyclopropyl-1H-benzimidazole-5-carboxamidine);
2,2'-methylenebis(N-allyl-1H-benzimidazole-5-carboxamidine);
2,2'-methylenebis(5-(5-((3aR,7aR)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazol-2-yl)-1H-benzimidazole);
2,2'-methylenebis(N-(2-adamantyl)-1H-benzimidazole-5-carboxamidine);
2,2'-methylenebis(N-cyclohexyl-1H-benzimidazole-5-carboxamidine);
2,2'-methylenebis(5-(imino(1,2,3,4-tetrahydro-2-isoquinolyl)methyl)-1H-benzimidazole);
2,2'-methylenebis(N-(3,3-diphenylpropyl)-1H-benzimidazole-5-carboxamidine and
2,2'-methylenebis(5-(iminopiperidinomethyl)-1H-benzimidazole);

Preferred compounds of the invention include

2,2'-Methylenebis(5-(3,4,5,6-tetrahydro-2-pyrimidinyl)-1H-benzimidazole)
2,2'-Methylenebis(5-((3aR,7aS)-3a,4,5,6,7,7a-hexahydro-1H- benzimidazol-2-yl)-1H-benzimidazole)
(±)-trans,trans-2,2'-Methylenebis(5-(3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole)
2,2'-Methylenebis(5-((3aR,7aR)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole)
2,2'-Methylenebis(5-((3aS,7aS)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole-2-yl)-1H-benzimidazole)
2,2'-Methylenebis(5-(4,4-dimethyl-2-imidazolin-2-yl)-1H-benzimidazole
2,2'-Methylenebis(N-cyclopropyl-1H-benzimidazole-5-carboxamidine)
2,2'-Ethylidenebis(5-(2-imidazolin-2-yl)-1H-benzimidazole)
2,2'-Methylenebis(N-allyl-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenebis(5-(4-ethyl)-2-imidazolin-2-yl)-1H-benzimidazole)
2,2'-Methylenebis(N-cyclopentyl-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenebis(N-(tetrahydro-2-furfuryl)-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenebis((±)trans-N-(2-phenyl-1-cyclopropyl)-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenebis(N-cyclohexyl-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenbis(N-cycloheptyl-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenebis(5-(4,5,6,7-tetrahydro-1H-1,3-diazepin-2-yl)-1H-benzimidazole)
2,2'-Methylenebis(5-(1,4,5,6-tetrahydro-5,5-dimethyl-2-pyrimidinyl)-1H-benzimidazole)
2,2'-Methylenebis(5-(3,4-dihydro-2-quinazolinyl)-1H-benzimidazole)
2,2'-Methylenebis(5-(iminopiperidinomethyl)-1H-benzimidazole)
2,2'-Methylenebis(5-(imino(1,2,3,4-tetrahydro-2-isoquinolyl)methyl)-1H-benzimidazole)
2,2'-Methylenebis(N-(2-adamantyl)-1H-benzimidazole-5-carboxamidine)
2,2'-(2,2'-Methylenebis(1H-benzimidazol-2,5-diyl))bis(1H-naphth(2,3-d)imidazole
2,2'-Methylenebis(5-(5-((3aR,7aR)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazol-2-yl)-1H-benzimidazole
2,2'-Methylenebis(N-benzhydryl-1H-benzimidazole-5-carboxamidine)
2,2'-Methylenebis(5-(aminomethyl)-1H-benzimidazole)

Especially preferred compounds of the invention include

2,2'-methylene bis(N-cyclopentyl-1H-benzimidazole-5-carboxamidine);
2,2'-methylene bis (N-tetrahydro-2-furfuryl-1H-benzimidazole-5-carboxamidine);
2,2'-methylenebis(5-(4,4-dimethyl-2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-methylenebis(5-(4-ethyl)-2-imidazolin-2-yl)-1H-benzimidazole);
2,2'-methylenebis(5-(1,4,5,6-tetrahydro-5,5-dimethyl-2-pyrimidinyl)-1H-benzimidazole);

their tautomers, stereoisomers and the pharmaceutically acceptable salts thereof.

The above definition of the compounds of formula (I) includes provisos to exclude certain compounds. The following references herein to compounds of formula (I) refer to those compounds defined above including the specified provisos. The following references herein to compounds of formula (I^1) refer to those compounds defined above by formula (I) without the specified provisos, in particular 2,2'-methylenebis (5-(2-imidazolin-2-yl)-1H-benzimidazole), (compound CC)

The references to compounds of formulae (I) and (I^1) include the pharmaceutically acceptable salts and physiologically functional derivatives of such compounds.

The compounds of formula (I^1) are potent inhibitors of HIV integrase and have utility in the treatment of immunodeficiency virus infections and AIDS in mammals, for example in humans, monkeys or cats.

The present invention further includes:

(a) A method for the prophylaxis or treatment of a viral infection in an infected host, for example, a mammal, including a human, which comprises administering to said host a therapeutically effective non-toxic amount of a compound of formula (I^1). According to an embodiment of this aspect of the invention, the viral infection is a retrovirus infection, including an immunodeficiency virus infection, in particular an HIV, SIV or FIV infection.

(b) Use of a compound of formula (I^1) in the manufacture of a medicament for the prophylaxis or treatment of a viral infection for an example a retrovirus infection in particular an HIV infection.

In yet another aspect of the present invention, there are provided compounds of formula (I^1) for the prophylaxis and treatment of Toxoplasma (e.g. Toxoplasma gondii) or Plasmodium (e.g. Plasmodium falciparum) infections.

Thus the present invention further includes:

(c) A method for the prophylaxis or treatment of a Toxoplasma or Plasmodium infection in an infected host, for example, a mammal, including a human, which comprises administering to said host a therapeutically effective non-toxic amount of a compound of formula (I^1).

(d) Use of a compound of formula (I^1) in the manufacture of a medicament for the prophylaxis or treatment of a Toxoplasma or Plasmodium infection.

In another aspect of the present invention, there are provided

(a) the compounds of formula (I) for use in therapy, more particularly for use as antiviral agents, for example, for the prophylaxis or treatment of a retrovirus infection, in particular an HIV infection;

(b) pharmaceutical formulations comprising at least one compound of formula (I) together with a pharmaceutically acceptable carrier therefor.

As used herein, the term "physiologically functional derivative" means any physiologically acceptable salt, ester, amide or salt of such ester, of a compound of formula (I) or (I^1) or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof. Such a physiologically functional derivative is within the scope of the invention.

Examples of pharmaceutically acceptable salts and physiologically acceptable derivatives according to the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_{1-4}alkyl). Pharmaceutically acceptable salts include salts of organic carboxylic acids such as acetic, fumaric, citric, lactic, tartaric, maleic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic acids and inorganic acids such as hydrochloric, hydrobromic, sulphuric, phosphoric and sulphamic acids.

For therapeutic use, salts of the above compounds will be pharmaceutically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

The compounds of formulas (I) and (I^1) may be employed alone or in combination with other therapeutic agents for the treatment of the above infections or conditions.

Examples of such further therapeutic agents which are effective for the treatment of human viral infections include carbocyclic nucleosides (for example, carbovir and (1S,4R)-4-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-ethanol), oxathiolane nucleoside analogues (for example, (-)-cis-1-(2- (hydroxymethyl)-1,3-oxathiolan-5-yl)-cytosine (3TC) and (-)-cis-5-fluoro-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl)cytosine (FTC)), 3'-azido-3'-deoxythymidine (zidovudine; AZT), other 2',3'-dideoxynucleosides, such as 2',3'-dideoxycytidine and 2',3'-dideoxyinosine, acyclic nucleosides (for example, acyclovir), 2',3'-didehydrothymidine, protease inhibitors, (for example, saquinavir), and interferons (for example, α-interferon). The component compounds of such combination therapy may be administered simultaneously, in either separate or combined formulations, or at different times, for example, sequentially, such that a combined effect is achieved.

Pharmaceutical formulations of the compounds of formulas (I) and (I^1) also referred to herein as active ingredients, may be administered for therapy to a mammal including a human ("the recipient") by any suitable route appropriate to the clinical condition to be treated; suitable routes include oral, rectal, nasal, topical (including buccal, sublingual and transdermal), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). It will be appreciated that the preferred route will vary with the condition, weight, age and sex of the recipient, the nature of the infection and the chosen active ingredient.

The amount of the active ingredient required for the treatment of the above named viral infections, will depend on a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician or veterinarian.

In general, a suitable dose for the treatment of each of the above named infections in a mammal, including a human, is in the range 3.0 to 120 mg per kilogram body weight of the recipient per day, preferably in the range 6 to 90 mg per kilogram body weight per day and most preferably in the range 15 to 60 mg per kilogram body weight per day. Unless otherwise indicated all weights of active ingredients are calculated as the parent compound of formulas (I) or (I^1) . In the case of a salt, ester or physiologically functional derivative of a compound of formulas (I) or (I^1) or a solvate of any thereof the figures would be increased proportionately. The desired dose is preferably presented as two, three, four, five, six, or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing from 10 to 1500 mg, preferably from 20 to 1000 mg, most preferably from 50 to 700 mg of active ingredient per unit dosage form. Alternatively, if the condition of the recipient so requires, the dose may be administered as a continuous infusion.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise at least one active ingredient, together with one or more acceptable carriers thereof and, optionally, one or more other therapeutic agents. Each carrier must be

"acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Formulations of the invention include those suitable for administration by any of the aforementioned routes which may conveniently be presented in unit dosage form and may be prepared by any method well know in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary, or paste or may be contained within liposomes.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (for example, povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxmethyl cellulose), or a surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile or to be soluble or effervescent when added to liquid. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for oral use may also include buffering agents designed to neutralize stomach acidity. Such buffers may be chosen from a variety of organic or inorganic agents such as weak acids or bases admixed with their conjugated salts.

A capsule may be made by filling a loose or compressed powder on an appropriate filling machine, optionally with one or more additives. Examples of suitable additives include binders such as povidone; gelatin, lubricants, inert diluents and disintegrants as for tablets. Capsules may also be formulated to contain pellets or discrete sub-units to provide slow or controlled release of the active ingredient. This can be achieved by extruding and spheronising a wet mixture of the drug plus an extrusion aid (for example microcrystalline cellulose) plus a diluent such as lactose. The spheroids thus produced can be coated with a semi-permeable membrane (for example ethyl cellulose, Eudragit WE30D) to produce sustained release properties.

Pharmaceutical formulations for topical administration according to the present invention may be formulated as an ointment, cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol or oil. Alternatively, a formulation may comprise a dressing such as a bandage or adhesive plaster impregnated with active ingredients and optionally one or more excipients or diluents.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution of 2) dissolved in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

For infections of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient in an amount of, for example, 0.075 to 20% w/w, preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active

ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base or as a water-in-oil base.

If desired, the aqueous phase of the cream base may include, for example, at least 40-45% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulphoxide and related analogues.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent. The ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored material, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert material such as gelatin and glycerin, or sucrose and acacia; and mouth-washes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or higher fatty alcohol (e.g. hard wax, European Pharmacopoeia) or triglycerides and saturated fatty acids (e.g. Witepsol).

Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

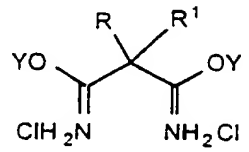
Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of formulas (I) and (I^1) may be produced by various methods known in the art of organic chemistry in general. The compound 2,2'-methylenebis(5-(2-imidazolin-2-yl)-1H-benzimidazole) may be prepared by the method of Fairley, T.A. et al., J. Med. Chem., 36(12), 1746-53 (1993). Starting materials are either known or readily available from commercial sources or may themselves be produced by known and conventional techniques.

The present invention further includes a process for the preparation of a compound of formula (I) or a salt or physiologically functional derivative of a compound of formula (I) or a solvate of any thereof which comprises:

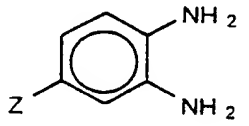
A. Reacting a diimino ether of formula (II)



(II)

wherein Y, which may be the same or different, is C_{1-12} alkyl (optionally substituted by one or more phenyl), C_{3-7} cycloalkyl, C_{3-6} alkenyl or phenyl

and R and R^1 are as defined for formula (I) with a compound of formula (III)



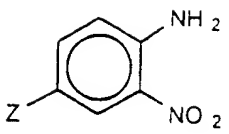
(III)

wherein Z is as defined hereinbefore. Preferably Y, in compounds of formula (II), is methyl, ethyl or propyl.

The reaction between the compounds of formulas (II) and (III) may be carried out conventionally, for example by heating in an anhydrous solvent such as acetic acid or ethanol.

Compounds of formula (II) may be prepared from the appropriate dicyano alkyl precursors by reaction with anhydrous hydrochloric acid in a mixture of the appropriate anhydrous alcohol, e.g. methanol or ethanol and a cosolvent such as tetrahydrofuran or dioxane, or in the alcohol alone.

Compounds of formula (III) may be prepared by reducing a compound of formula (IV)

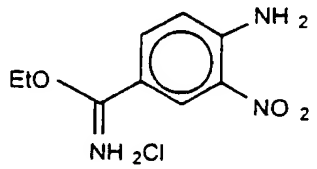


(IV)

wherein Z is as defined hereinbefore.

The reduction of compounds of formula (IV) may be carried out by methods known in the art, most preferably catalytic hydrogenation, for example with palladium on carbon, in a solvent such as ethanol/water either ambiently or under pressure.

Compounds of formula (IV) may be prepared by reacting an appropriate amine or diamine with an imino ether of formula (V):

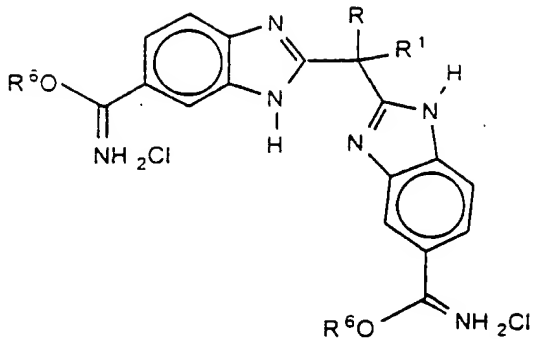


(V)

Typically, the amine or diamine and imino ether of formula (V) are heated together in a solvent such as ethanol.

The imino ether of formula (V) may be prepared from commercially available 4-amino-3-nitrobenzonitrile by treatment with anhydrous HCl and anhydrous alcohols, such as ethanol, in cosolvents such as tetrahydrofuran or dioxane, or in the alcohol alone.
or

B. Alternatively, compounds of formula (I) may be prepared by reacting a diimino ether of formula (VI):

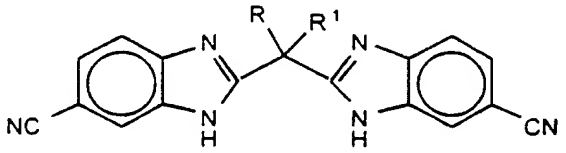


(VI)

wherein R and R^1 are as defined for formula (I) and R^6 is C_{1-6} alkyl, for example ethyl,

with an appropriate amine or diamine (e.g, cyclopentylamine, cis-1,2-diaminocyclohexane, piperidine or 1,2-diaminobutane) in an anhydrous solvent such as ethanol.

Compounds of formula (VI) may be prepared from a compound of formula (VII)



(VII)

wherein, R and R^1 are as defined for formula (I) by reacting with anhydrous hydrochloric acid in a mixture of the appropriate anhydrous alchohol, e.g. methanol or ethanol and a cosolrent such as tetrahydrofuran or dioxane, or in the alcohol alone.

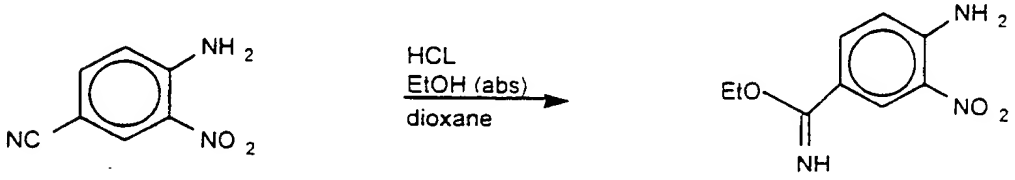
Compounds of formula (VII) may be prepared by condensing 3,4-diaminobenzonitrile with a diimino ether of formula (II), by heating in an anhydrous solvent such as glacial acetic acid.

The compounds of formula (I) may be converted into pharmaceutically acceptable salts in a conventional manner. In the case of amino substituents, the salts may be obtained by treatment with an appropriate acid.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. ^1H NMR and C,H,N elemental analyses were consistent with structure in all examples.

Example 1 2,2'-Methylenebis(5-(3,4,5,6-tetrahydro-2-pyrimidinyl)-1H-benzimidazole) (Compound A)

a) Ethyl 4-amino-3-nitrobenzimidate



1 2

A stirred mixture of 4.2g (25mmoL) of 4-amino-3-nitrobenzonitrile 1 in a solution of 600 mL of absolute ethanol and 100 mL of dioxane was heated to 60° C under nitrogen for 1h. The mixture was filtered, and the residual homogenous solution was cooled in an ice bath as HCl gas was bubbled into it for 1h. The mixture was allowed to stand at room temperature (RT) for 9 days whereupon the crystals were collected, washed with ether and dried affording 3.8g (62%) of the title compound (hereinafter referred to as imino ether 2). mp 223-225° C

b) 2-(4-Amino-3-nitrophenyl)-3,4,5,6-tetrahydro-pyrimidine

A stirred mixture of 6.2g (25mmoL) of imino ether 2 and 6.3 mL (75 mmoL) of 1,3-propane diamine in 200 mL of absolute ethanol was warmed to 60° C for 15h. The solution was then refluxed for 4h, cooled to RT, and spin evacuated *in vacuo* affording a brown-yellow semi-solid. High vacuum evacuation overnight afforded a yellow solid which was dissolved in 300 mL of absolute ethanol, filtered and allowed to stand for several hours. The yellow precipitate was collected and subsequently refluxed with acetonitrile for 30 min. The resultant solid was collected, washed twice with diethyl ether and dried affording 4.1g (74%) of the title compound mp > 250° C.

c) 2-(3,4-Diaminophenyl)-3,4,5, 6-tetrahydro-pyrimidine

A heterogenous mixture comprised of 2.3g of the tetrahydropyrimidine product of stage b) and 1.15g of 10 % palladium on carbon (50% wet with water) in a solution of 130 mL of ethanol and 20 mL of deionized water was hydrogenated at RT and 3 atm on a Parr apparatus for 3h. The mixture was filtered and concentrated by spin evaporation *in vacuo*.

The residual solid was diluted with 500 mL of ethanol and concentrated again. The pink crystals were collected, washed with diethyl ether and dried affording 1.9g of the title compound mp > 250° C.

d) Compound A

A stirred mixture of 4.2g (18 mmoL) of the diimino ether, diethyl malonimidate hereinafter referred to as the "diimino ether 5" (Kenner, G.W. et al. *J. Chem Soc.*, **1943,** 574.) and 1.6g of the diamine product of stage c) in 75 mL of glacial acetic acid was warmed to 60° C for 19h. The solution was filtered while warm and allowed to cool to RT. This mixture was diluted with ethanol, filtered and treated with a solution of ethanolic HCL. After stirring for 1h, the mixture was diluted with a 2:1 solution of diethyl ether and ethyl acetate until a precipitate formed. This precipitate was collected, washed three times with diethyl ether and dried affording bis-benzimidazole A as a pale green solid. mp > 250° C.

Example 2 2,2'-Methylenebis(5-((3aR,7aS)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole) (Compound B)

a) (±)-cis-2-(4-Amino-3-nitrophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A solution of 10.6g (42.9 mmoL) of imino ether 2 and 5.0g (42.9 mmoL) of *cis* -1,2-diaminocyclohexane in 250 mL of absolute ethanol was warmed to reflux and therein maintained for 19h. The mixture was cooled, filtered and the filtrate was concentrated

under reduced pressure to afford a yellow solid. This solid was dissolved in a minimal amount of distilled water, and was subsequently treated with concentrated ammonium hydroxide until a precipitate formed. This precipitate was collected, washed with water, then a 1:1 solution of diethyl ether/ethyl acetate, followed by exhaustive washing with diethyl ether. The material was then dried affording 6.6g (67%) of the title compound as a granular yellow solid. mp>250° C.

b) (±)-cis-2-(2,3-Diaminophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A suspension of 3.5 g (15 mmoL) of the nitro aniline product of stage a) and 1.0 g of 10% palladium on activated carbon (wet, Degussa type) in 180 mL of absolute ethanol was hydrogenated in a Parr bottle at c.22°C and at c.50 psi for 5h. The resultant black suspension was diluted with absolute ethanol, was filtered and concentrated under reduced pressure to afford a straw colored solid. This solid was diluted with 500 mL of absolute ethanol and was again concentrated under reduced pressure to afford 2.8 g (94%) of the title product as a tan solid. In order to prevent decomposition, this material was quickly submitted to further synthetic elaboration in its entirety.

c) Compound B

A suspension of 2.3 g (10 mmoL) of the diamine product of stage b) and 1.2 g (5 mmoL) of diimino ether 5 in 120 mL of glacial acetic acid was refluxed for 17h. The dark brown mix was cooled, filtered and treated with ethyl acetate until the mixture became turbid. This solution was filtered and again treated with ethyl acetate until turbid. This solution was again filtered, and was treated with 300 mL of diethyl ether. The tan solid was washed exhaustively with diethyl ether, collected and dried. The resultant solid was dissolved in absolute ethanol and acidified with an ethanolic solution of HCl. This precipitate was collected, washed exhaustively with diethyl ether, ethyl acetate and again with ether, was collected and dried. This solid was dissolved in a minimal amount of distilled water, and was subsequently treated with concentrated ammonium hydroxide until a precipitate formed. This precipitate was collected, washed with water, then a 1:1

soultion of diethyl ether:ethyl acetate, followed by exhaustive washing with diethyl ether and dried affording 1.4 g (25%) of B as a tan solid. mp>250° C.

Example 3 (±)-trans,trans-2,2'-Methylenebis(5-(3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole) (Compound C)

a) (±)-trans-2-(4-Amino-3-nitrophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A solution of 10.6g (42.9 mmoL) of imino ether 2 and 5.0g (42.9 mmoL) of (±) *trans* - 1,2-diaminocyclohexane in 300 mL of absolute ethanol was warmed to reflux and therein maintained for 22h. The mixture was cooled, filtered and the filtrate was concentrated under reduced pressure to afford a yellow solid. This solid was refluxed in a minimal amount of acetonitrile and collected. Exhaustive washing with diethyl ether afforded 7.8 g (79%) of the title compound as a yellow solid. mp>250° C.

b) (±)-trans-(2,3-Diaminophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A suspension of 3.5 g (15 mmoL) of the (±) nitro aniline product of stage a) and 1.0 g of 10% palladium on activated carbon (wet, Degussa type) in 180 mL of absolute ethanol was hydrogenated in a Parr bottle at c.22°C and at c.50 psi for 5h. The resultant black suspension was diluted with absolute ethanol, was filtered and concentrated under reduced pressure to afford a straw colored solid. This solid was diluted with 500 mL of absolute ethanol and was again concentrated under reduced pressure to afford 2.9 g (95%) of the title compound as a tan solid. In order to prevent decomposition, this material was quickly submitted to further synthetic elaboration in its entirety.

c) Compound C

A suspension of 2.3 g (10 mmoL) of the (±) diamine product of stage b) and 1.2 g (5 mmoL) of diimino ether 5 in 120 mL of glacial acetic acid was refluxed for 17h. The dark brown mix was cooled, filtered and treated with ethyl acetate until the mixture became turbid. This solution was filtered and again treated with ethyl acetate until turbid. This

solution was again filtered, and was treated with 300 mL of diethyl ether. The tan solid was washed exhaustively with diethyl ether, collected and dried. This solid was refluxed in a minimal amount of acetonitrile, was collected, washed with ether and dried. This procedure was repeated three times affording bisbenzimidazole (±) C as a light tan powder. mp>250° C.

Example 4 2,2'-Methylenebis(5-((3aR,7aR)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole) (Compound D)

a) (3aR,7aR)-trans-2-(4-Amino-3-nitrophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A solution of 10.6g (42.9 mmoL) of imino ether 2 and 5.0g (42.9 mmoL) of (R,R) *trans* - 1,2-diaminocyclohexane in 250 mL of absolute ethanol was warmed to reflux and therein maintained for 19h. The mixture was cooled, filtered and the filtrate was concentrated under reduced pressure to afford a yellow solid. This solid was dissolved in a minimal amount of distilled water, and was subsequently treated with concentrated ammonium hydroxide until a precipitate formed. This precipitate was collected, washed with water, then a 1:1 solution of diethyl ether/ethyl acetate, followed by exhaustive washing with diethyl ether. The material was then dried affording 6.6g (59%) of the title compound as a yellow solid. mp>250° C.

b) (3aR,7aR)-trans-(3,4-Diaminophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A suspension of 3.5 g (15 mmoL) of the (R,R) nitro aniline product of stage a) and 1.0 g of 10% palladium on activated carbon (wet, Degussa type) in 180 mL of absolute ethanol was hydrogenated in a Parr bottle at c.22°C and at c.50 psi for 5h. The resultant black suspension was diluted with absolute ethanol, was filtered and concentrated under reduced pressure to afford a straw colored solid. This solid was diluted with 500 mL of absolute ethanol and was again concentrated under reduced pressure to afford 2.8 g (94%) of the title compound as a tan solid. In order to prevent decomposition, this material was quickly submitted to further synthetic elaboration in its entirety.

Compound D

A suspension of 2.3 g (10 mmoL) of the (R.R) diamine product of stage b) and 1.2 g (5 mmoL) of diimino ether 5 in 120 mL of glacial acetic acid was refluxed for 20h. The dark brown mix was cooled, filtered and treated with ethyl acetate until the mixture became turbid. This solution was filtered and again treated with ethyl acetate until turbid. This solution was again filtered, and was treated with 300 mL of diethyl ether. The tan solid was washed exhaustively with diethyl ether, collected and dried. The resultant solid was dissolved in absolute ethanol and acidified with an ethanolic solution of HCl. This precipitate was collected, washed exhaustively with diethyl ether, ethyl acetate and again with ether, was collected and dried affording 1.6 g (20%) of bisbenzimidazole D as a tan solid. mp>250° C.

Example 5 2,2'-Methylenebis(5-((3aS,7aS)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole-2-yl)-1H-benzimidazole) (Compound E)

a) (3aS,7aS)-2-(4-Amino-3-nitrophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A solution of 2.16 g (8.77 mmol) of imino ether 2 and 1.00 g (8.77 mmol) of 1*S*,2*S*-diaminocyclohexane in 10 mL of absolute ethanol was heated at reflux for 6 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Water (10 mL) was added to the residual yellow solid followed by concentrated ammonium hydroxide (20 mL). The mixture was filtered, the solid material taken up in MeOH and the homogenous solution treated with decolorizing carbon. Filtration through celite was followed by concentration under reduced pressure. The yellow solid was stirred in diethyl ether and filtered affording 1.94 g (7.46 mmol, 84% yield) of imidazoline title compound, mp 220 °C.

b) (3aS,7aS)-(3,4-Diaminophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A Parr bottle was charged with the product of stage a) (1.00 g, 3.85 mmol), 5% Pd/C (50 mg), and absolute ethanol (60 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 16 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound E

A solution of 434 mg (1.88 mmol) of diimino ether 5 and the diamine product of stage b) (3.85 mmol) in 10 mL of glacial acetic acid was heated at 70 °C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Water (10 mL) was added to the residual yellow solid followed by concentrated ammonium hydroxide (20 mL). The mixture was filtered, the solid material taken up in MeOH and the homogenous solution treated with decolorizing carbon. Filtration through celite was followed by concentration under reduced pressure. The yellow solid was stirred in diethyl ether and filtered affording 710 mg (1.32 mmol, 70% yield) of bisbenzimidazole E. mp >250 °C.

Example 6 2,2'-Methylenebis(5-(4,4-dimethyl-2-imidazolin-2-yl)-1H-benzimidazole (Compound F)

a) 2-(4-Amino-3-nitrophenyl)-4,4-dimethyl-2-imidazoline

A solution of 3.8 g (15.5 mmoL) of imino ether 2 and 5 mL of 1,2-diamino-2-methyl propane in 150 mL of absolute ethnaol was refluxed for 19h. The mixture was cooled and filtered. This solution was diluted with 400 mL of diethyl ether and the resultant solid was collected and discarded. The filtrate was concentrated and placed under vacum overnight. This material was diluted with ether, the resultant solid was collected, washed exhaustively with ether, filtered and dried to afford 1.8g (50%) of the title compound as a yellow solid.

b) 2-(3,4-Diaminophenyl)-4,4-dimethyl-2-imidazoline

A Parr bottle was charged with the nitroaniline product of stage a) (2.01 g, 8.59 mmol), 5% Pd/C (429 mg), and absolute ethanol (43 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 16 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound F

A solution of 945 mg (4.09 mmol) of diimino ether 5 and the diamine product of stage b) (8.59 mmol) in 22 mL of glacial acetic acid was heated at 70 °C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (120 mL) was added to the filtrate and the heterogenous mixture filtered. The solid residue was dissolved in hot 2-propanol (50 mL) and the solution cooled to room temperature. Diethyl ether (150 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole F as a light brown powder (1.24 g, 2.18 mmol, 53% yield). mp >250 °C; ^{1}H NMR [200 MHz] (DMSO-d6) 8.30 (s, 2H), 7.85 (dd, 2H, J=1.2, 8.6 Hz), 7.72 (d, 2H, J=8.6 Hz), 4.65 (s, 2H), 3.72 (s, 4H), 1.45 (s, 12H).

Elemental analysis: Calculated for $C_{25}H_{28}N_8 \cdot 2.0HCl \cdot 1.10\ H_2O \cdot 0.6(CH_3)_2CHOH$: C, 56.54; H, 6.55; N, 19.68; Cl 12.45.
Found: C, 56.41; H, 6.30; N, 19.52; Cl 12.41.

Example 7 2,2'-Methylenebis(N-cyclopropyl-1H-benzimidazole-5-carboxamidine) (Compound G)

a) 4-Amino-N-cyclopropyl-3-nitrobenzamidine

A solution of 4.9 g (20.0 mmoL) of imino ether 2 and 5 mL of cyclopropyl amine were refluxed in 170 mL of absolute ethanol for 22h. The mixture was cooled and the volume

was reduced by one half on the rotovap. The material was subsequently treated with 300 mL of diethyl ether. The resultant solid was collected and dried, refluxed in acetonitrile, collected, washed exhaustively with ether, filtered and dried affording 4.2 g (82%) of the title compound as a yellow solid.

b) 3,4-Diamino-N-cyclopropylbenzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (2.57 g, 10.0 mmol), 5% Pd/C (500 mg), and absolute ethanol (150 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 16 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound G

A solution of 1.10 g (4.76 mmol) of diimino ether 5 and the diamine product of stage b) (10.0 mmol) in 25 mL of glacial acetic acid was heated at 70°C for 16h. The mixture was cooled to room temperature and filtered. Diethyl ether (120 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (50 mL) and the solution cooled to room temperature. Diethyl ether (150 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole G as a light brown powder (1.94 g, 2.18 mmol, 71% yield). mp 200 °C (dec).

Example 8 2,2'-Methylenebis(N-hexyl-1H-benzimidazole-5-carboxamide) (Compound H)

a) 4-Amino-N'-hexyl-3-nitrobenzamidine

A solution of 6.5 g (26.5 mmoL) of imino ether 2 and 15 mL of hexyl amine were refluxed in 200 mL of absolute ethanol for 22h. The mixture was cooled and treated with 500 mL of a 4:1 solution of diethyl ether /hexanes solution. The resultant solid was

collected and dried, refluxed in acetonitrile, collected, washed exhaustively with ether, filtered and dried affording 5.3g (64%) of the title compound as a yellow solid. mp 192-195 °C.

b) 3,4-Diamino-N'-hexyl-benzamidine

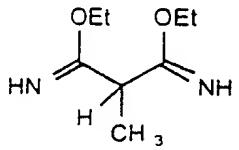
A Parr bottle was charged with the nitroaniline product of stage a) (2.07 g, 6.88 mmol), 5% Pd/C (344 mg), and absolute ethanol (34 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 16 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound H

A solution of 757 mg (3.28 mmol) of diimino ether 5 and the diamine product of stage b) (6.88 mmol) in 42 mL of glacial acetic acid was heated at 70 °C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (120 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (50 mL) and the solution cooled to room temperature. Diethyl ether (150 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole H as a light brown powder (1.58 g, 2.58 mmol, 79% yield). mp 205 °C (dec).

Example 9 2,2'-Ethylidenebis(5-(2-imidazolin-2-yl)-1H-benzimidazole) (Compound I)

a) Diethyl 2-methylmalonimidate



20

A solution of methylmalononitrile (1.00 g, 12.5 mmol) in absolute ethanol (1.46 mL, 25.0 mmol) was cooled to 0 °C. Dry HCl gas was bubbled through the solution for 1 h. The pasty mixture was sealed and refrigerated for 48 h. The resultant homogenous solid was placed under high vacuum for 1 h. Recovered 2.86 g (11.6 mmol, 93% yield) of the diimino ether 20 as a white powder.

b) 2-(4-Amino-3-nitrophenyl)-2-imidazoline

A solution of 5.21 g (21.2 mmol) of imino ether 2 and 7.1 mL (106 mmol) of ethylene diamine in 42 mL of absolute ethanol was heated at reflux for 20 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Water (50 mL) was added to the residual yellow solid followed by concentrated ammonium hydroxide (100 mL). The mixture was filtered and dried under high vacuum to recover the imidazoline title compound (4.14 g, 20.1 mmol, 95% yield) as a yellow solid. mp 198 ° C.

c) 2-(3,4-Diaminophenyl)-2-imidazoline

A Parr bottle was charged with the nitroaniline product of stage b) (1.00 g, 4.85 mmol), 5% Pd/C (100 mg), and absolute ethanol (25 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 16 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil

that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

d) Compound I

A solution of 158 mg (0.646 mmol) of diimino ether 20 and the diamine product of stage c) (1.36 mmol) in 3.4 mL of glacial acetic acid was heated at 70 °C for 16 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Water (3 mL) was added to the residual solid followed by concentrated ammonium hydroxide (6 mL). The homogenous solution was concentrated to a volume of about 1 mL under reduced pressure. Absolute ethanol (5 mL) was added followed by diethyl ether (10 mL) to effect precipation. Filtration afforded the bisbenzimidazole I (44 mg, 0.080 mmol, 12% yield) as a green solid. mp 240 °C (dec).

Example 10 2,2'-Methylenebis(N-allyl-1H-benzimidazole-5-carboxamidine) (Compound J)

a) 3,4-Diaminobenzonitrile

Ten grams of 4-amino-3-nitro-benzonitrile was dissolved in 250 ml of hot absolute ethanol, poured over 500 mg of 5% palladium on carbon in a 500 ml Parr flask and hydrogenated under 60 psi pressure. After approximately 1 hour, hydrogenation was complete. the solution was filtered through celite, and the solution rotovapped to dryness yielding brown crystals of the title compound. The yield was close to 100%. mp = 143 °C.

b) 2,2'-Methylenebis(5-cyano-1H-benzimidazole)

7.8 grams (2 equivalents) of the 3,4-diaminobenzonitrile product of stage a) was dissolved in approximately 146 ml of glacial acetic acid giving an amber solution and placed under nitrogen. 7.3 grams (1 equivalent) of the diimino ether 5 was added, but did not go into solution. The mixture was heated overnight, approximately 20 hrs, at 70 °C on an oil bath.

The reaction mixture was filtered giving cream colored crystals and a deep red filtrate. The filtrate was rotavapped to dryness, yielding brown crystals and converted to the free base by suspending in water, adding an equivalent volume of ammonium hydroxide and filtering. The crystals were further purified by dissolving in methanol, filtering, rotavapping to dryness, washing with ether and drying, giving 3.26 grams of brown crystals for a yield of 24% pure title compound, mp = 289-294 °C.

c) Diethyl 2,2'-Methylenebis(1H-benzimidazole-5-carboximidate)

1.1 grams of the dicyanobisbenzimidazole product of stage b) was dissolved in 1.1 liters of hot absolute ethanol, filtered and placed in a round bottom flask purged with nitrogen. Approximately 92 mls of dioxane was added and the reaction flask placed in an ice bath. HCl gas was bubbled through while the temperature was kept between 20° and 30°C. The solution turned a bluish green almost immediately, and within five minutes cream colored crystals began to form. The reaction mixture saturated with HCl after one hour: HCl was bubbled through an additional hour and the mixture left under nitrogen over night.

A total of 4 liters of ethyl ether was added to precipitate the crystals, which were washed with ether and dried giving a 74% yield of the title compound, mp = 239-245 °C.

d) Compound J

A solution of the product of stage c) (463 mg, 1.00 mmol) and allylamine (750 mL, 10.0 mmol) in absolute ethanol (10 mL) was heated at reflux for 5 h. The solution was cooled to room temperature and diethyl ether (20 mL) added to precipitate the product. Recrystallization from hot 2-propanol and water yielded compound J (130 mg, 0.238 mmol, 24% yield). mp >250 °C.

Example 11 2,2'-Methylenebis(5-(4-ethyl)-2-imidazolin-2-yl)-1H-benzimidazole) (Compound K)

A 100 ml round bottom three necked flask was flame dried under nitrogen and 0.410 grams of the bisbenzimidazole diiminoether product of stage c) of Example 10 was dissolved in 20 ml of absolute ethanol. Five equivalents of 1,2-diaminobutane (Lancaster Chemical #12495) was added and the reaction mixture lightly refluxed for 24 hours. Ether was added, causing the formation of a black substance. The ether was poured off and the substance added to 25 ml distilled water. Thirty ml of ammonium hydroxide was added, causing white crystals to be formed. The crystals were filtered, washed with water and dissolved in methanol which was filtered and concentrated. The resultant crystals were washed with ether and dried, yielding 125 mg of slightly impure crystals. The HCl salt was formed by dissolving the crystals in a few drops of absolute ethanol and adding 1 ml of 7.1 N ethanolic HCl. The resulting crystals were purified by redissolving in methanol, filtering, concentrating, washing with ether and drying. NMR and mass spec showed the presence of the desired product bis-benzimidazole K. Elemental analysis showed complexation of 4 moles of HCl, 2.2 of H_2O and 0.3 of ethanol. mp = 134 °C (d) ^1H NMR [200 MHz] (DMSO-d_6) 11.0 (m, 4H), d 8.58 (m, 2H), d 8.07 (m, 2H), d 7.91 (m, 2H), d 5.05 (m, 2H), d 4.37 (m, 2HO, d 4.13 (m, 2H), d 3.70 (m, 2H), d 1.7 (m, 4H), d 0.99 (t, 6H, J=6.9 Hz).

Elemental analysis: Calculated for $C_{25}H_{28}N_8 \cdot 2.2\ H_2O \cdot 4.0\ HCl \cdot 0.3$ ETOH: C, 46.08; H, 6.02; N, 17.51. Found: C, 48.12; H 5.71; N, 17.23.

Example 12 2,2'-Methylenebis(N-cyclopentyl-1H-benzimidazole-5-carboxamidine) (Compound L)

a) 4-Amino-N-cyclopentyl-3-nitrobenzamidine

A yellow suspension of 9.8 g (40 mmoL) of imino ether 2 in 250 mL of absolute ethanol was treated with 4.4 mL (44 mmoL) of cyclopentylamine and the resultant mixture was refluxed for 19 h. The suspension was cooled to RT, filtered and the solution was diluted with a c. 3:1 solution of diethyl ether and hexanes and allowed to stir for 1 h. The solid

was collected, exhaustively washed with diethyl ether, collected and dried to afford 5.9 g (59%) of the cyclopentyl amidine title compound as an orange-yellow solid.

b) 3,4-Diamino-N-cyclopentylbenzamidine

A Parr bottle was charged with the product of stage a) (2.04 g, 7.16 mmol), 10% Pd/C (180 mg), and absolute ethanol (36 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 16 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound L

A solution of 788 mg (3.41 mmol) of diimino ether 5 (diethyl malonimidate, Kenner, G.W. et al. *J. Chem Soc.*, **1943**, 574.) and the diamine product of stage b) (7.16 mmol) in 40 mL of glacial acetic acid was heated at 70 °C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole L as a brown powder (1.59 g, 2.59 mmol, 76% yield. ^{1}H NMR [200 MHz] (DMSO-d$_6$) 9.69 (d, 2H, J=7.1 Hz), 9.50 (s, 2H), 9.13 (s, 2H), 8.01 s, 2H), 7.72 (d, 2H, J=8.4 Hz), 7.58 (d, 2H, J=8.4 Hz), 4.76 (s, 2H), 4.22 (m, 2H), 2.05 (m, 4H), 1.73 (br s, 8H), 1.56 (m, 4H).

Elemental analysis: Calculated for $C_{27}H_{32}N_8 \cdot 2.6\ HCl \cdot 1.2\ H_2O \cdot 0.4\ (CH_3)_2CHOH \cdot 0.1\ NH_4Cl$: C, 55.13; H, 6.66; N, 18.47; Cl 15.58.
Found: C, 55.11; H, 6.75; N, 18.52; Cl 15.52.

Example 13 2,2'-Methylenebis(N-(tetrahydro-2-furfuryl)-1H-benzimidazole-5-carboxamidine) (Compound M)

a) 4-Amino-3-nitro-N-(tetrahydrofurfuryl)benzamidine

To a stirred suspension of 5.0 g (20 mmol) of imino ether 2 in 250 mL of anhydrous ethanol was added 2.5 mL (24 mmol) of tetrahydrofurfurylamine. The reaction was refluxed for 19 h, cooled to room temperature and filtered. This solution was diluted with diethyl ether and the resultant solid was collected, washed thoroughly with diethyl ether, and dried to afford 3.8 g (60%) of the title compound as a yellow solid.

b) 3,4-Diamino-N-(tetrahydrofurfuryl)benzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (2.20 g, 7.14 mmol), 10% Pd/C (180 mg), absolute ethanol (71 mL), and water (7 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 2 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was used without further purification.

c) Compound M

A solution of 785 mg (3.40 mmol) of the diimino ether 5 (diethyl malonimidate) and the diamine product of stage b) (7.14 mmol) in 18 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum affordeed bisbenzimidazole M as a brown powder (1.64 g, 2.55 mmol, 75% yield). ^{1}H NMR [200 MHz] (DMSO-d_6) 9.88 (s, 2 H), 9.51 (s, 2 H), 9.09 (s, 2 H), 8.01 (s, 2 H), 7.71 (d, 2 H, J = 8.4 Hz), 7.58 (d, 2 H, J = 8.4 Hz), 4.69 (s, 2 H), 4.13 (m, 2 H), 3.81 (m, 2 H), 3.67 (m, 2 H), 3.62-3.45 (comp. 4 H), 2.01 (m, 2 H), 1.92-1.78 (comp, 4 H), 1.62 (m,2 H); Elemental analysis: Calculated for

$C_{27}H_{32}N_8O_2 \cdot 2.1HCl \cdot 1.1H_2O \cdot 0.5C_2H_4O_2 \cdot 0.3NH_4Cl$: C, 52.30 H. 6.19; N, 18.08; Cl 15.23: Found: C. 52.36; H. 6.22; N, 18.06; Cl 13.23.

Example 14 2,2'-Methylenebis((±)trans-N-(2-phenyl-1-cyclopropyl)-1H-benzimidazole-5-carboxamidine) (Compound N)

a) (±)-trans-4-amino-3-nitro-N-(2-phenyl-1-cyclopropyl)benzamidine

A solution of 4.5 g (26 mmoL) of phenylcyclopropylamine hydrochloride in 200 mL of anhydrous ethanol was treated with 26 mL (26 mmoL) of a 1.0 M THF solution of potassium tert-butoxide and the resultant white suspension was stirred at room temperature for 30 minutes. The mixture was then treated with 6.2 g (25 mmoL) of imino ether 2 and the resultant suspension was warmed at c.50_C for 19h. The mixture was cooled to room temperature and filtered. The filtrate was treated with a 3:1 solution of hexanes/diethyl ether until a precipitate formed. This solid was collected, washed with ether and dried affording 3.9 g (54%) of the title cyclopropyl amidine compound.

b) (±)-trans-3,4-Diamino-N-(2-phenyl-1-cyclopropyl)benzamidine

A Parr bottle was charged with the product of stage a) (2.01 g, 5.74 mmol), 10% Pd/C (140 mg), absolute ethanol (57 mL) and water (6 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 2 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound N

A solution of 6.31 g (2.73 mmol) of diimino ether 5 and the diamine product of stage b) (10.0 mmol) in 14 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (120 mL) was added to the filtrate and the heterogenous mixutre filtered. The dark solid was dissolved in hot 2-propanol (50 mL) and the solution cooled to room temperature. Diethyl ether (150 mL) was added to

precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole N as a light brown powder (1.13 g, 1.64 mmol, 60% yield).

Example 15 2,2'-Methylenebis(N-cyclohexyl-1H-benzimidazole-5-carboxamidine) (Compound O)

a) 4-Diamino-N-cyclobexyl-3-nitrobenzamidine

A suspension of 6.2 g (25 mmoL) of imino ether 2 in 250 mL of absolute ethanol was treated with 3.2 mL (28 mmoL) of cyclohexylamine and the resultant yellow solution was refluxed for c.60 h. The suspension was then cooled to room temperature, filtered, and the filtrate was treated with a 4:1 solution of hexanes/diethyl ether until a precipitate formed. This solid was collected. washed with ether and dried affording 4.9 g (66%) of the title amidine compound.

b) 3,4-Diamino-N-cyclohexylbenzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (2.03 g, 6.79 mmol), 10% Pd/C (170 mg), and absolute ethanol (34 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 3 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound O

A solution of 747 mg (3.23 mmol) of diimino ether 5 and the diamine product of stage b), (6.79 mmol) in 17 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole O as a brown powder (1.53 g, 2.14 mmol, 66% yield).

Example 16 2,2'-Methylenbis(N-cycloheptyl-1H-benzimidazole-5-carboxamidine) (Compound P)

a) 2-(4-Amino-3-nitrophenyl)-4,5,6,7-tetrahydra-1H-1,3-diazapine

A solution of 5.0g (20 mmol) of imino ether 2 and 3.0 mL (23 mmol) of cycloheptylamine were refluxed in 120 mL of absolute ethanol for 22 h. The solution was cooled to RT to obtain a solid which was collected by filtration then discarded. The filtrate was treated with 600 mL of a 5:1 solution of diethyl ether/hexanes. The resultant solid was collected, washed exhaustively with ether, and dried affording 1.35g (22%) of the title compound as a yellow solid.

b) 2-(3,4-Diaminophenyl)-4,5,6,7-tetrahydro-1H-1,3-diazapine

A Parr bottle was charged with the nitroaniline product of stage a) (1.41 g, 4.46 mmol), 10% Pd/C (110 mg), and absolute ethanol (22 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 3 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound P

A solution of 491 mg (2.12 mmol) of diimino ether 5 and the diamine product of stage b) (4.46 mmol) in 11 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole P as a brown powder (1.15 g, 1.79 mmol, 84% yield).

Example 17 2,2'-Methylenebis(5-(4,5,6,7-tetrahydro-1H-1,3-diazepin-2-yl)-1H-benzimidazole) (Compound Q)

a) 4-Amino-N-cycloheptyl-3-nitrobenzamidine

To a suspension of 5.0 g (20 mmol) of imino ether 2 in 250 mL of absolute ethanol was added 2.4 mL (24 mmol) of 1,4-diaminobutane (free base) and the heterogeneous solution was refluxed for 22 h. giving a clear yellow solution. The solution was cooled to room temperature, diluted with 675 mL diethyl ether, filtered, and the precipitate set aside. The filtrate was diluted with 3 L of diethyl ether, filtered, washed with diethyl ether, and dried overnight. The solid was stirred in ammomium hydroxide, filtered, washed with 1:4 hexanes: diethyl ether and dried overnight, yielding 1.82 g (37%) of the title compound as orange crystals.

b) 3,4-Diamino-N-cycloheptyl benzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (1.70 g, 6.94 mmol), 10% Pd/C (170mg), absolute ethanol (69 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 2 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidifed on standing. The isolated product was used without further purification.

c) Compound Q

A solution of 763 mg (3.30 mmol) of diimino ether 5 and the diamine product of stage b) in 20 mL of glacial acetic acid was heated at 70_C for 3 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded the bisbenzimidazole Q as a rust coloured powder (1.33 g, 2.21 mmol, 67% yield).

Example 18 2,2'-Methylenebis(5-(1,4,5,6-tetrahydro-5,5-dimethyl-2-pyrimidinyl)-1H-benzimidazole) (Compound R)

a) 2-(4-Amino-3-nitrophenyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine

To a suspension of 9.0 g (36.6 mmol) of the imino ether 2 in 200 mL of absolute ethanol was added 5.0 mL (40 mmol) of 2,2-dimethyl-1,3-propanediamine and the mixture was refluxed for 20 h. The reaction mixture was cooled to room temperature and filtered. The yellow crystals were washed with diethyl ether and dried overnight yielding 9.8 g (94%) of the title compound.

b) 2-(3,4-Diaminophenyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine

A Parr bottle was charged with the nitroaniline product of stage b) (2.26 g, 7.93 mmol), 10% Pd/C (200 mg), absolute ethanol (40 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 2 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound R

A solution of 872 mg (3.78 mmol) of diimino ether 5 and the diamine product of stage b) (7.93 mmol) in 20 mL of glacial acetic acid was heated at 70_C for 3 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole R as a brown powder (1.58 g, 2.47 mmol, 65% yield). ^{1}H NMR [200 MHz] (DMSO-d_6) 10.26 (s, 4 H), 8.08 (s, 2 H), 7.71 (d, 2 H, J = 8.4 Hz), 7.63 (d, 2 H, H = 8.4 Hz), 4.69 (s, 2 H), 3.20 (s, 8 H), 1.03 (s,6H); Elemental analysis: Calculated for

$C_{27}H_{32}N_8 \cdot 2.OHCl \cdot 1.3H_2O.0.8(CH_3)_2CHOH \cdot 0.5NH_4Cl$: C, 55.20; H, 7.09; N, 18.61; Cl 13.85: Found: C, 55.17; H, 7.06: N, 18.57; Cl 15.52.

Example 19 2,2'-Methylenebis(5-(3,4-dihydro-2-quinazolinyl)-1H-benzimidazole) (Compound S)

a) 2-(4-Amino-3-nitrophenyl)-3,4-dihydroquinazoline

A solution of 9.8 g (40 mmol) of imino ether 2 and 5.5g (44 mmol) of 2-aminobenzylamine were refluxed in 200 mL of absolute ethanol for 22h. The solution was cooled to RT. The resultant solid was collected, washed exhaustively with diethyl ether and dried affording 9.6g (72%) of the title compound as a yellow solid.

b) 2-(3,4-Diaminophenyl)-3,4-dihydroquinazoline

A Parr bottle was chrged with the nitroaniline product of stage a) (2.01 g, 6.05 mmol), 5% Pd/C (200 mg), absolute ethanol (30 mL) and water (10 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 1 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound S

A solution of 772 mg (3.34 mmol) of diimino ether 5 and the diamine product of stage b) (6.05 mmol) in 15 mL of glacial acetic acid was heated at 60_C for 20 h. The mixture was cooled to room temperature and filtered. The solid was taken up in water (10 mL) and concentrated ammonium hydroxide (20 mL) was added. The mixture was filtered, the solid material taken up in MeOH and the homogenous solution treated with decolorizing carbon. Filtration through celite was followed by concentration under reduced pressure. The residual solid was stirred in diethyl ether and filtered affording 912 mg (1.65 mmol, 57% yield) of bisbenzimidazole S. mp 225_C (dec).

Example 20 2,2'-Methylenebis(5-(iminopiperidinomethyl)-1H-benzimidazole) (Compound T)

a) 1-(4-Amino--imino-3-nitrobenzyl)piperidine

A suspension of 9.8 g (40 mmoL) of imino ether 2 in 200 mL of absolute ethanol was treated with 4.4 mL (44 mmoL) of piperidine and the resultant homogenous solution was refluxed for 20h. The yellow solid was collected, washed with diethyl ester, and dried affording 6.5 g (61%) of the title amidine compound.

b) 1-(3,4-Diamino--iminobenzyl)piperidine

A Parr bottle was charged with the nitroaniline product of stage a) (2.00 g, 7.02 mmol), 5% Pd/C (351 mg), and absolute ethanol (35 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 6 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine title compound (100% yield) as a brown oil that solidified on standing. The isolated product was somewhat unstable and was used without further purification.

c) Compound T

A solution of 772 mg (3.34 mmol) of diimino ether 5 and the diamine product of stage b) (7.02 mmol) in 18 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (50 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (50 mL) and the solution cooled to room temperature. Diethyl ether (150 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole T as a light brown powder (1.55 g, 2.18 mmol, 76% yield). mp 220 _C (dec).

Example 21 2,2'-Methylenebis(5-(imino(1,2,3,4-tetrahydro-2-isoquinolyl)methyl)-1H-benzimidazole) (Compound U)

a) 2-(4-Amino--imino-3-nitrobenzyl)-1,2,3,4-tetrahydro-isoquinoline

To a suspension of 5.0 g (20 mmol) of the imino ether 2 in 250 mL of absolute ethanol was added 2.8 mL (22 mmol) of 1,2,3,4- tetrahydroisoquinoline and the mixture refluxed 20 h. The solution was cooled to room temperature and filtered. The filtrate was diluted with 100mL of 1:2 hexanes:diethyl ether and the heterogeneous solution filtered. The yellow crystals were washed with diethyl ether, and dried overnight, giving 2.3 g (33.8%) of the title compound.

b) 2-(3,4-Diamino--imino benzyl)-1,2,3,4-tetrahydroisoquinoline

A Parr bottle was charged with the nitroaniline product of stage a) (1.64 g, 4.82 mmol), 10% Pd/C (140 mg), and absolute ethanol (28 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 3 h. The solution was filtered through celite and concentrated *in vacuo* to afford the diamine (100% yield) as a brown oil that solidified on standing. The isolated product was used without further purification.

c) Compound U

A solution of 530 mg (2.30 mmol) of diimino ether 5 and the diamine product of stage a) (4.82 mmol) in 12 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (50 mL) was added to the filtrate and the solution cooled to room temperature. Diethyl ether (150 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole compound U as a brown powder (1.55 g, 1.41 mmol. 61% yield).

Example 22 2,2'-Methylenebis(N-(2-adamantyl)-1H-benzimidazole-5-carboxamidine) (Compound V)

a) N-(2-Adamantyl)-4-amino-3-nitrobenzamidine

A homogenous solution of 4.7 g (25 mmoL) of 2-adamantylamine hydrochloride in 250 mL of absolute ethanol was treated with 26 mL (26 mmoL) of a 1.0 M THF solution of potassium tert-butoxide. The resultant white suspension was stirred for 15 minutes and treated with 6.2 g (25 mmoL) of imino ether 2. The yellow suspension was warmed to c.50_C for sixty hours, cooled to room temperature and filtered. This solution was treated with a 3:1 hexanes/ether solution until a precipitate appeared. The solid was collected. washed with ether, and dried affording 5.8 g (74%) of the title adamantylamidine compound.

b) N-(2-Adamantyl)-3,4-diaminobenzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (2.07 g, 5.90 mmol), 10% Pd/C (150 mg), and absolute ethanol (29 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 3 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) asa brown oil that soldified on standing. The isolated product was used without further purification.

c) Compound V

A solution of 649 mg (2.81 mmol) of diimino ether 5 and the diamine product of stage b) (5.90 mmol) in 15 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Diethyl ether (80mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (75 mL) and the solution cooled to room temperature. Diethyl ether (30 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole V as a brown powder (760 mg, 0.987 mmol. 35% yield).

Example 23 2,2'-(2,2'-Methylenebis(1H-benzimidazol-2,5-diyl))bis(1H-naphth(2,3-d)imidazole (Compound W)

a) 2-(4-Amino-3-nitrophenyl)-1H-naphth(2,3-d)imidazole

To a suspension of 3.8 g (24 mmol) of 2,3-diaminonapthalene in 250 mL of absolute ethanol was added 5.0 g (20 mmol) of imino ether 2. The heterogeneous mixture was refluxed for 20 h, cooled to room temperature, filtered and the brown crystals washed with diethyl ether and dried overnight yielding 3.8 g (59.3%) of the title compound.

b) 2-(3,4-Diaminophenyl)-1H-naphth(2,3-d)imidazole

A Parr bottle was charged with the nitroaniline product of stage a) (2.06 g, 6.46 mmol), 10% Pd/C (160 mg), absolute ethanol (65 mL) and water (6 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 5 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a yellow solid. The isolated product was used without further purification.

c) Compound W

A solution of 711 mg (3.08 mmoL) of diimino ether 5 and the diamine product of stage b) (6.46 mmol) in 16 mL of glacial acetic acid was heated at 70_C for 16 h. The mixture was cooled to room temperature and filtered. Exposure to high vacuum afforded bisbenzimidazole W as a brown powder (1.87 g, 2.51 mmol, 81% yield).

Example 24 2,2'-Methylenebis(5-(5-((3aR,7aR)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazol-2-yl)-1H-benzimidazole (Compound X)

a) cis-2-(4-Amino-3-nitrophenyl)-5-(3a,5,6,7,7a-hexahydro-1H-benzimdazol-2-yl)-1H-benzimidazole

A solution of 1.06 g (4.32 mmol) of imino ether 2 and 1.23 g (4.32 mmol) of the diamine product of stage b) of Example 2 in 13 mL of glacial acetic acid was heated at 70_C for

18h. The reaction mixture was cooled to room temperature and filtered to recover the title compound as an orange powder (1.42 g, 2.95 mmol, 68% yield).

b) cis-2-(3,4-Diaminophenyl)-5-(3a,5,6,7,7a-hexahydro-1H-benzimidazol-2-yl)-1H-benzimidazole

A Parr bottle was charged with the product of stage a) (1.00 g, 2.11 mmol), 10% Pd/C (110 mg), absolute ethanol (21 mL) and water (5.3mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 6 h. The solution was diluted with water (10 mL) to bring the product into solution and filtered through celite. Concentration *in vacuo* afforded the title diamine compound (100% yield) as a brown solid. The isolated product was used without further purification..

c) Compound X

A solution of 231 g (1.00 mmol) of diimino ether 5 and the diamine product of stage b) (2.11 mmol) in 25 mL of glacial acetic acid was heated at 110_C for 36h. The mixture was cooled to room temperature and filtered. The bis-benzimidazole X was recovered as a light brown powder (320 g, 0.311 mmol, 31% yield).

Example 25 2,2'-Methylenebis(N-benzhydryl-1H-benzimidazole-5-carboxamidine) (Compound Y)

a) 4-Amino-N-benzhydryl-3-nitrobenzamidine

To a suspension of imino ether 2 in 110 mL of absolute ethanol 3.5 mL (22 mmol) of aminodiphenylmethane was added and refluxed for 18 h. The reaction flask was cooled to room temperature and the contents concentrated under reduced pressure. The residue was boiled in 400 mL of isopropanol for 10 minutes and filtered. The filtrate was diluted with 4300 mL of hexanes and filtered. The crystals were washed with diethyl ether and dried under vacuum overnight affording 0.82 g (9.8%) of the title compound as yellow crystals.

b) 3,4-Diamino-N-Benzhydrylbenzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (690 mg, 1.7 mmol), 10% Pd/C (42 mg), and absolute ethanol (17 mL). The mixture was shaken under an atmosphere of hydrogen (60 psi) for 6 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidified on standing. The isolated product was used without further purification.

c) Compound Y

A solution of 190 mg (0.81 mmol) of diimino ether 5 and the diamine product of stage b) (1.7 mmol) in 4.3 mL of glacial acetic acid was heated at 70_C for 16h. The mixture was cooled to room temperature and filtered. Diethyl ether (25 mL) was added to the filtrate and the heterogenous mixture filtered. The dark solid was dissolved in hot 2-propanol (25 mL) and the solution cooled to room temperature. Diethyl ether (75 mL) was added to precipitate the product which was recovered by filtration. Exposure to high vacuum afforded bisbenzimidazole Y as a light green powder (410 mg, 0.52 mmol, 64% yield).

Example 26 2,2'-methylenebis(N,N^1-dibutyl-1H-benzimidazole-5-carboxamidine)

a) 4-Amino-N,N^1-dibutyl-3-nitrobenzamidine

To a stirred suspension of 6.2 g (25 mmol) of imino ether 2 in 195 mL of anhydrous methanol was added 50 mL (506 mmol) of butylamine. The reaction was refluxed for 44 h. The reaction was cooled to room temperature and filtered. This solution was diluted with 3000 mL of diethyl ether and the resultant solid was collected. The solid was then purified via a recrystallisation from 600 mL of acetonitrile, washed thoroughly with diethyl ether, and dried to afford 2.6 g (31.7%) of the title compound as a yellow solid.

b) 3,4-Diamino-N,N^1-dibutylbenzamidine

A Parr bottle was charged with the nitroaniline product of stage a) (1.26 g, 3.83 mmol), 10% Pd/C (150 mg), and methanol (19 mL). The mixture was shaken under an

atmosphere of hydrogen (60 psi) for 3 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title diamine compound (100% yield) as a brown oil that solidified on standing. The isolated product was used without further purification.

c) Compound Z

A solution of 442 mg (1.92 mmol) of diimino ether 5 and the diamine product of stage b) (3.83 mmol) in 9.6 mL of glacial acetic acid was heated at 110_C for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in 2-propanol (20 mL) and added to concentrated NH_4OH (150 mL) with stirring. The solid was removed by decanting and washed with water (2 x 100 mL). The residue was taken up in MeOH (100 mL) and concentrated *in vacuo*. Exposure to high vacuum afforded bisbenzimidazole Z as a brown solid (780 mg, 1.36 mmol, 71% yield).

Example 27 2,2'-Methylenebis(5-(aminomethyl)-1H-benzimidazole) (Compound AA)

A Parr bottle was charged with the bisnitrile product of stage b) of Example 10 (298 mg, 1.00 mmol), PtO_2 (50 mg), absolute ethanol (50 mL), con HCl (2 mL), and water (10 mL). The mixture was shaken under an atmosphere of hydrogen (55 psi) for 2 h. The solution was filtered through celite and concentrated *in vacuo* to afford the title bis-benzimidazole AA (430 mg, 0.887 mmol, 89% yield) as a green powder.

Example 28 2,2'-Methylenebis(5-(1-ethyl-2-imidazolin-2-yl)-1H-benzimidazole) (Compound BB)

a) 2-(4-Amino-3-nitrophenyl)-1-ethyl-2-imidazoline

To a stirred mixture of 2.0 g (8.1 mmol) of imino ether 2 in 60 mL of absolute ethanol at 0_C was added 1.44 g (16.3 mmol) N-ethylethylene diamine. The mixture was refluxed for 20h whereupon the solvent was removed. The paste washed with water and ammonium hydroxide, filtered and dried to afford 1.56g (93%) of the title compound.

b) 2-(3,4-Diaminophenyl)-1-ethyl-2-imidazoline

A suspension of 1.5 g (6.6 mmol) of the product of stage a) and 10.8g of 5% palladium on carbon catalyst in 250 mL absolute ethanol was shaken under hydrogen at 30 psi for 30 min after H_2 uptake ceased. The mixture was filtered and the catalyst washed with methanol. Solvent removal afforded 1.26g (93%) of the title diamine compound as a clear oil.

c) Compound BB

A stirred mixture of 0.7 g (3 mmol) of the diimino ether 5 and 1.2 (5.9 mmol) of the diamine in 100 mL of glacial acetic acid was warmed at 100_C for 18h whereupon the solvent was removed *un vacuo*. The residue was diluted with 5 mL of i-PrOH and added dropwise to rapidly stirring NH_4OH whereupon the brown solid was filtered, washed with H_2O and dried to afford 1.4 (54%) of the bis-benzimidazole BB. mp 170-173_C.

The term 'active ingredient' as used in the examples means a compound of formulas (I) or (I^1) or a pharmaceutically acceptable salt, or physiologically functional derivative of a compound of formulas (I) or (I^1) or a solvate of any thereof.

Example A

Formulation B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose	150	-
(c)	Avicel PH 101	60	6
(d)	Povidone B.P.	5	9
(e)	Sodium Starch Glycollate	20	12
(f)	Magnesium Stearate	5	3
		490	280

Formulation C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following formulations, D and E, are prepared by direct compression of the admixed ingredients. The lactose in formulation E is of the direct compression type (Dairy Crest - "Zeparox").

Formulation D

	mg/tablet
Active ingredient	250
Pregelatinised Starch NF15	150
	400

Formulation E

	mg/tablet
Active ingredient	250
Lactose	150
Avicel	100
	500

Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the ingredients (below) with a solution of povidone followed by the addition of magnesium stearate and compression.

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53

(d)	Povidone B.P.	28
(e)	Magnesium Sterate	7
		700

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

Example B

Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of Formulation D in Example A above and filling the mixture into a two-part hard gelatin capsule. Formulation B (infra) is prepared in a similar manner.

Formulation B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Formulation C

		mg/capsule
(a)	Active ingredient	250
(b)	Macrogol 4000 B.P.	350
		600

Formulation D

	mg/capsule
Active ingredient	250

Lecithin	100
Arachis Oil	100
	450

Capsules of formulation D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients (a), (b) and (c) using an extruder, followed by spheronisation of the extrudate and drying. The dried pellets are then coated with the release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose B.P.	125
(d)	Ethyl Cellulose	13
		513

Example C

Injectable Formulation

Formulation A

Active ingredient	0.200g
Hydrochloric acid solution, O.1M, or	
Sodium hydroxide solution, 0.1M q.s. to pH	4.0 to 7.0
Sterile water q.s. to	10 ml

The active ingredient is dissolved in most of the water at 35°C-40°C and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or sodium hydroxide as appropriate. The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile10 ml amber glass vial (type 1) and sealed with sterile closures and overseals.

Formulation B

Active ingredient	0.125
Sterile, pyrogen-free, pH 7 phosphate buffer, q.s. to	25 ml

Antiviral Activity: HIV Assay

Anti-HIV activity of compounds of formula (I) was determined using the method of Averett D.R., 1989, J.Virol. Methods, 23, 263-276, by measuring the ability of the compound to reverse the cytopathic effect of HIV infection. This was determined by a quantitative assessment of cell growth monitored at the fifth day post infection by a propidium iodide dye uptake test. MT4 cells were incubated with 100XTCID$_{50}$ of HIV-1 (strain 3B) or HIV-2 (strain ZY) for one hour prior to addition of the compound in six different concentrations varying from 2 to 200 M. The cells were allowed to incubate for five days at 37°C. On day 5, NP-40, a detergent, was added to a final concentration of 0.5% immediately prior to analysis. Cell number was determined using a method which measures the fluorescence of a dye (propidium iodide) which binds to DNA. Since the amount of DNA is directly proportional to cell number, this fluorescence assay is an indication of cell growth. While uninfected cells double in cell number several times during the five days duration of the assay, HIV-infected cells grow very little, if at all. A compound which reverses the cytopathic effect of HIV would allow for rapid cell growth, approaching that of the mock-infected cells.

The antiviral effect of a compound is reported as an IC$_{50}$, i.e. as the inhibitory concentration that would produce a 50% decrease in the HIV-induced cytopathic effect.

This effect is measured by the amount of compound in DMSO solution required to restore 50% of the cell growth of HIV-infected MT4 cells compared to uninfected MT4 cell controls.

Anti-HIV-1 Activity of Representative Compounds

Example No.	Compound	IC_{50} (μM)*	n
1	A	90.8	2
2	B	4.8	5
3	C	3.9	9
4	D	3.9	1
5	E	3.0	1
6	F	6.5	1
7	G	20.6	4
8	H	2.6	2
9	I	37.9	2
10	J	9.6	1
11	K	6.7	1
12	L	3.2	3
13	M	4.5	1
18	R	9.6	2
-	CC	37.0	1

*Average of "n" assays

Activity against Toxoplasma Gondii (Tg)

Compounds according to the invention were examined for the ability to inhibit the formation of visible plaques (rings of fibroblast destruction) produced by Toxoplasma gondii.

Human fibroblasts (Hf) of passage of less than 30 were plated into 12 well cluster plates. The wells of the cluster plates received 3 ml of medium VA-13 with 10% adult bovine serum and were plaqued in a humidified chamber with 5% DC2 balance air. All medium contained 100 units/ml penicillin G and 100 ug/ml streptomycin sulfate. The wells were 2.2cm diameter. After the Hf had grown to confluence (usually less than 7 days) the bovine medium was poured off and replaced with 2ml of VA-13 medium containing 0.3% bovine serum albumin which had been inoculated with Tg to produce zero, 20, 200 and 2000 Tg per well. The exact number of Tg used per well was subjectively changed for each experiment depending on the relative freshness of the parasite source culture and the assumed vitality of the infecting Tg. The Tg were allowed to enter the cells fore one to 4 hours before the drug was added in 1 ml of VA-13-albumin at 3/2 X concentration. The cultures were allowed to grow 5 days without being disturbed. On the fifth day the cultures were examined with phase contrast microscopy and the presence of Tg and Tg-produced plaques verified. The wells were scored as containing Tg or not, and any other effects noted as such as damage to the Hf monolayer or reduced size of the plaque.

The medium was poured off and the wells fixed with 100% methanol for 5 min. The wells were air dried and stained for 30 min giemsa and the plaque count determined on select cultures and wells to determine the IC_{50} of the tested compounds. The results are as follows:-

Example No.	Compound	IC_{50}(M)
2	B	5
4	D	5

Activity against Plasmodium Falciparum

Compounds according to the invention were tested for their activity against Plasmodium Flaciparum in accordance with the method described by Hudson A.T. et al. Drugs Exptl. Clin. Res. XVII (9), 427-435 (1991).

The results are as follows:-

Example No.	Compound	IC_{50}(M)
1	A	12
2	B	<5
3	C	<5
4	D	<5
10	J	<5

Cytotoxicity

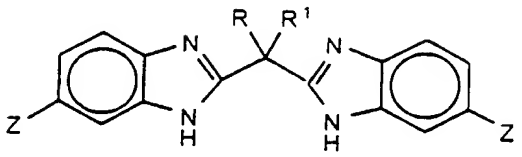
Compounds according to the invention were tested for the inhibition of growth of human T-cells (Molt 4), B-cells (IM9) and CEM cells by the method of Averett, D.R.., J. Virol. Methods, **23**, 263-276 (1989). Cells were grown as described in Prus, K.L., et al., Cancer Res., **50**(6), 1817-1821 (1990). Results are as follows:-

		% of Cells Surviving at 200M		
Example No	Compound	IM9	CEM	Molt 4
6	F	53	132	70
11	K	-	98	69
12	L	-	91	66
13	M	75	115	91
18	R	56	91	96

IC_{50} values were >200M for all of the above compounds.

CLAIMS

1. Compounds of general formula (I)

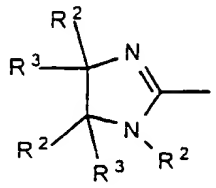


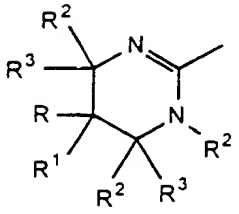
(I)

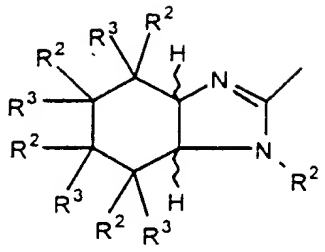
wherein,

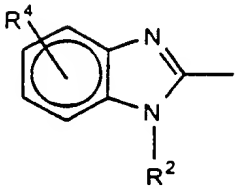
R and R^1, which may be the same or different, are hydrogen, fluoro, hydroxyl, amino, C_{1-6} alkoxy, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl;

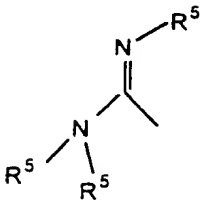
Z is selected from a group consisting of

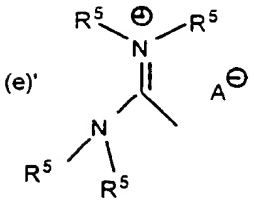
(a) 

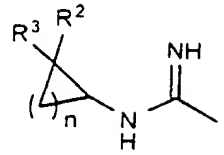
(b) 

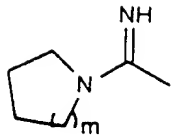
(c) 

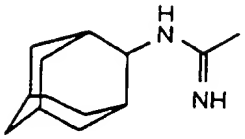
(d) 

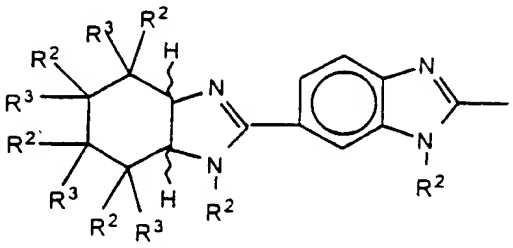
(e) 

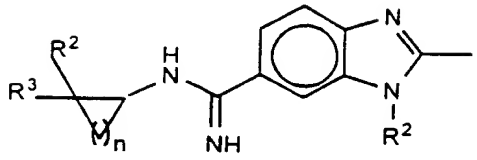
(e)' 

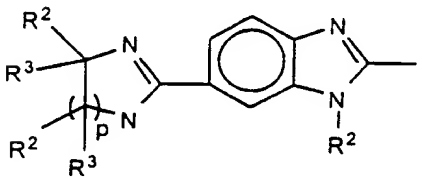
(f) 

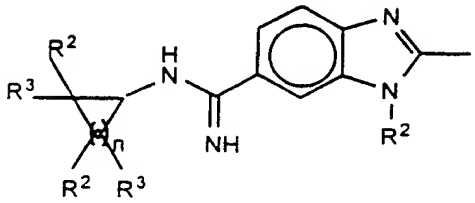
(g) 

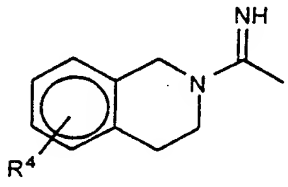
(h) 

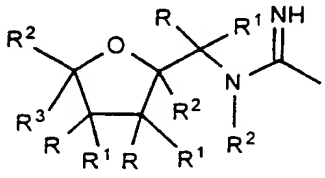
(i) 

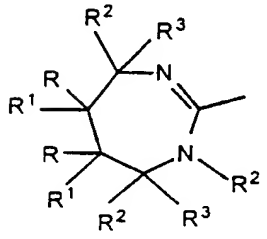
(j) 

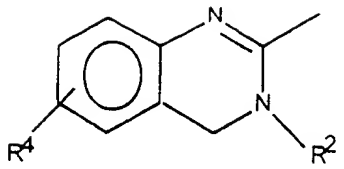
(k) 

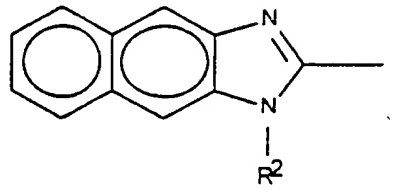
(j') 

(l) 

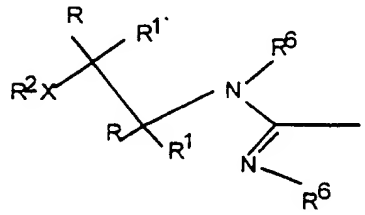
(m) 

(n) 

(o) 

(p) 

(q) $-CH_2NH_2$ (providing R and R^1 do not both represent hydrogen)

(r) 

wherein

m is 0, 1 or 2;

n is 1, 2, 3, 4 or 5;

p is 1, 2 or 3;

R^2, and R^3, which may be the same or different, are hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl, phenyl, -COOH, $-COOR^{2a}$, $-CON(R^{2a})_2$ or $-(CH_2)n$ X R^{2a} (wherein R^{2a} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl, n is 1,2,3,4 or 5 and X is as defined below);

R^4 is hydrogen, halo, amino, C_{1-4} alkoxy, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or phenyl;

R^5, which may each be the same or different, is C_{1-6} alkyl substituted by one or more phenyl groups (e.g. diphenylmethyl) or by a heterocyclic group comprising a 5- or 6- membered saturated or unsaturated ring containing 1 or 2 heteroatoms selected from the group consisting of O, N and S optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, amino, nitro or halo; C_{3-7} cycloalkyl; C_{2-6} alkenyl; phenyl; hydrogen; or a C_{3-7} carbocyclic ring optionally substituted by R^2 and R^3 (wherein R^2 and R^3 are as hereinbefore defined); provided that the R^5 groups are not all hydrogen;

R^6, which may each be the same or different, is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl C_{1-6} alkyl or $-(CH_2)n\ X\ R^2$ wherein n and R^2 are as hereinbefore defined;

X is O, S or NH;

A^- is a physiologically acceptable anion; and

R and R^1 (in formulae (b), (n), (m) or (r)) are as hereinbefore defined;

with the provisos that (i) when Z is (a) or (b), R and R^1 (in formula (b)) and R^2 and R^3 are not all hydrogen; (ii) when Z is (n), R, R^1, R^2 and R^3 are not all hydrogen;

or a pharmaceutically acceptable salt thereof; or a physiologically functional derivative thereof.

2. Compounds as claimed in claim 1 wherein Z is (a), (b) or (e),

3. Compounds as claimed in claim 1 or claim 2 wherein R^2 and R^3 are each hydrogen.

4. Compounds as claimed in any of claims 1 to 3 for use in therapy.

5. Compounds as claimed in claim 4 for use in the prophylaxis or treatment of a retrovirus infection.

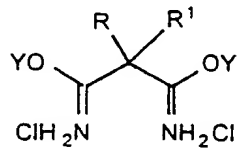
6. Pharmaceutical formulations comprising at least one compound as claimed in any of claims 1 to 3 together with a pharmaceutically acceptable carrier therefor.

7. A method for the prophylaxis or treatment of a viral infection in an infected host which comprises administering to said host a therapeutically effective non-toxic amount of compound (I) (as defined in claim 1 but not subject to the specified provisos) or a pharmaceutically acceptable salt or a physiologically functional derivative thereof.

8. Use of a compound of formula (I) (as defined in claim 1 but not subject to the specified provisos) or a pharmaceutically acceptable salt or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a viral infection.

9. A process for the preparation of compounds of formula (I) (as defined in claim 1) which comprises:-

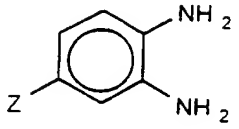
A. reacting a diimino ether of formula (II)



(II)

wherein Y, which may be the same or different, is C_{1-12} alkyl (optionally substituted by one or more phenyl), C_{3-7} cycloalkyl, C_{3-6} alkenyl or

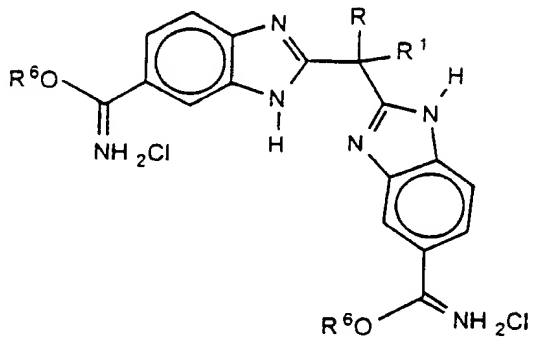
phenyl, and R and R^1 are as defined for formula (I) with a compound of formula (III)



(III)

wherein Z is as defined for formula (I); or

B. reacting a diimino ether of formula (VI):



(VI)

wherein R and R^1 are as defined for formula (I) and R^6 is C_{1-6} alkyl with an appropriate amine or diamine in an anhydrous solvent.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PC /GB 94/02051

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D235/20 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,94 08580 (THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL) 28 April 1994 see claims 1-18 ---	1-8
Y	US,A,4 324 794 (RESEARCH TRIANGLE INSTITUTE) 13 April 1982 see claims 1-5 ---	1-8
Y	ANTIMICROB. AGENTS CHEMOTHER., vol.26, no.4, 1984 pages 591 - 593 R.D. TIDWELL ET AL. 'Suppression of Respiratory Syncytal Virus Infection in Cotton Rats by Bis(5-Amidino-2-Benzimidazolyl)Methan' * entire document * --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 1994	-4. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CO ERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANTIMICROB. AGENTS CHEMOTHER., vol.37, no.8, 1993 pages 1713 - 1716 R.R. TIDWELL ET AL. 'Activity of Cationically Substituted Bis-Benzimidazoles against Experimental Pneumocytis carinii Pneumonia' see table 1 ---	1-8
Y	ANTIMICROB. AGENTS CHEMOTHER., vol.19, no.4, 1981 pages 649 - 656 E.J. DUBOVI ET AL. 'Inhibition of Respiratory Syncytial Virus-Host Cell Interactions by Mono- and Diamidines' see table 1 ---	1-8
Y	ANTIMICROB. AGENTS CHEMOTHER., vol.37, no.12, 1993 pages 2668 - 2673 C.A. BELL ET AL. 'Structure-Activity Studies of Dicationically Substituted Bis-Benzimidazoles against Giardia lamblia: Correlation of Antigiardial Activity with DNA Binding Affinity with DNA Binding Activity and Giardial Topoisomerase II Inhibition' see table 2 ---	1-5
Y	J. CLIN. INVEST., vol.82, no.6, 1988 pages 2011 - 2016 S.L. VONDERFECHT ET AL. 'Protease Inhibitors Suppress the In Vitro and In Vivo Replication of Rotavirus' * entire document * -----	1-8

2

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Intern al Application No
PCT/GB 94/02051

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9408580	28-04-94	AU-B-	5299593	09-05-94
		CA-A-	2104196	14-04-94
US-A-4324794	13-04-82	US-A-	4397863	09-08-83